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EXAMINER

LI, BAO Q

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 10/22/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/888,235

Applicant(s)

BLONDER ET AL.

Examiner

Bao Qun Li

Art Unit

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-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 August 2002.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-147 is/are pending in the application.
- 4a) Of the above claim(s) 45-147 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### DETAILED ACTION

Claims 1-147 are pending.

#### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-44 on paper No. 8 is acknowledged.
2. Claims 45-147 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No.8. Applicants are requested to cancel the claims drawn to the non-elected groups.

#### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:  
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.
4. Claims 1-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claim 1 is vague and indefinite in that the intended "an immunogen composition" "a biocompatible polymer" and "a liquid vehicle" are not defined. The claim is interpreted in light of the specification; however, the limitation in the specification cannot read into the claims. In addition, the term "at least" in claim 1 is a relative term, which renders the claim indefinite. The term "at least" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. If applicants wish to claim a range of temperatures, please amend the claim to the precise temperature range that is intended. This affects the dependent claims 2-44.
6. Claim 2 is vague and indefinite in that the metes and bounds of the temperature below 40°C are not defined. Is -20°C intended? This affects the dependent claims 3-44.

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7. Claim 4 is unclear for recitation that composition is in the different form at least, when the composition is in different temperature range. The word “at least” is a relative word, which fails to define what other element(s) is required for reaching the condition of the claimed immunogenic composition. Therefore, the claims are considered as indefinite.

8. Claims 15, 20, 21, 23 and 24 are vague in that the use of a relative term of “derived”. Since the specification does not provide a standard for ascertaining the requisite degree of derivation and the term of “derivation” has many interpretation, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore the claim is considered as indefinite.

9. Claims 15-30 are unclear for recitation that the relative word “at least”. Because there is no up-limitation of the phrase of “at least”, are 10 antigens intended? Therefore, the claims are considered as indefinite.

10. Claims 4 and 7 are unclear in that the metes and bounds of the first temperature and the second temperature are not defined. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). If applicants are wish to claim a range of temperatures, please amend the claim to the precise temperature range that is intended.

11. Claim 32 is infinite in that the metes and bounds of products of microorganisms are not defined. The claim is interpreted in light of the specification, however, the specification does not teach and define what the product of microorganisms are.

12. Moreover, the phrase “such as” in the claim 32 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

### ***Claim Rejections - 35 USC § 112***

13. Claims 1-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the copolymer Fluronic F127®/Chitosan as an adjuvant for formulating the tetanus toxin and to induce an enhanced immune response, does not reasonably provide enablement for using any or all polymer plus any or all adjuvants to get an enhanced immune response with any or all antigens. The specification does not enable any person skilled

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in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case, the specification only teach that the use of Fluronic F127®/Chitosan as adjuvant to delivery the tetanus toxin and get an enhanced immune response in mice. However, the specification does not teach that the Fluronic F127®/Chitosan is able to produce an enhanced immune response if it is used as an adjuvant for delivering any or all antigen as claimed in claims 15-32.

Applicants are reminded that the field is unpredictable because different antigens have different characteristics and behave differently. Applicants do not provide any more evidence that support that any or all antigen formulated with any or all copolymer of  $\text{HO}(\text{C}_2\text{H}_4\text{O})_b(\text{C}_3\text{H}_6\text{O})_a(\text{C}_2\text{H}_4\text{O})_b\text{H}$  or  $\text{H}(\text{OC}_2\text{H}_2\text{CH}_2)_b(\text{OCHCH}_2)\text{CH}_3\text{a}(\text{OC}_2\text{H}_2\text{CH}_2)_b\text{OH}$  ( $\text{C}_3\text{H}_6\text{O}$ ) in combination with any or all adjuvants, rather than chitosan is able to induce an enhanced immune response in vivo. 132 ✓

Hence, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim.

### ***Double Patenting***

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-32, 34-37 and 44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 13-23 of copending Application No. 09/602,654. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claimed an immunogenic composition comprising an antigen, the same biocompatible polymer and adjuvant, wherein the copolymer make immunogenic composition to change the phase from liquid to the gel form when the temperature is switch from the lower range of 1-20 °C to the higher range of 25-37 °C. Although the claims word differently in the two applications, the scope of the claimed invention is overlapping.

#### ***Claim Rejections - 35 USC § 102***

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-32, 38-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Balasubramanian et al. (a) (US Patent No. 6,086,899A).

Patent “899” teaches a composition comprising a polypropylene/polyxyethylene block polymer block, an immunogenic antigen and an adjuvant, wherein the high molecular weight of copolymer are useful as general surfactant to assist the antigen to be dissolved and absorbed by the host and display an enhanced biological efficacy as vaccine adjuvants. The block copolymer is consisting of polyxyethylene (POE, C<sub>2</sub>H<sub>4</sub>O), which is hydrophilic, and polyxypropylene (POP, C<sub>3</sub>H<sub>6</sub>O), which is hydrophobic. The block copolymer is built on a propylene glycol initiator. The biologically active copolymers have the following general formulation

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$\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ , wherein the “b” represents a number such that the molecular weight of the POP ( $\text{C}_3\text{H}_6\text{O}$ ) is approximately 7000-20,000 Daltons and the POE is between approximately 1%-40% by molecular weight. The antigen that can be used in the said vaccine composition include both DNA virus and RNA virus, bacterial antigen, tumor antigen, other microbial antigens, allergens, and other protein antigen, such as tetanus toxoid, peptide antigen etc (see col. 9, line 50 through col. 11, line 64). The composition further contains surfactant substances, such as Tween 80 (claim 9). Patent “899” also discloses a method of modifying an immune response to an antigen in a human or animal comprising administering the antigen admixed with an adjuvant, wherein the adjuvant consists of a polypropylene/polyxyethylene block polymer (see claim 10) and Qui-A saponin etc. Moreover, Patent “899” teaches that variety of routes, including, but not limited to, intramuscular injection, intravenous injection, intraperitoneal injection, oral, rectal, vaginal, sublingually, and nasally, can be used for administering the composition comprising such polyethylene/polyxypropylene block copolymer (line 65 on col. 11 through line 3 on col. 12. Utilization of the composition comprising the said copolymer greatly enhances and prolongs the immune response (see Figures 9 and 23-24). Therefore, the claimed invention is anticipated by the cited prior art.

***Claim Rejections - 35 USC § 102***

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-31 and 43-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Ron et al. (WO 98/06438A2).

Ron et al. Teach to use a heat sensitive polyalkylene copolymer as an immunogenic pharmaceutical vehicle to deliver many pharmaceutical compositions including many pathogenic antigens. The said vehicle is a block copolymer with different oxyalkylene units having a capacity of a reversible gelation at body temperature (25-40°C) (see line 11-24 on page 11). At least one polyalkylene unit is polyxypropylene ( $\text{C}_3\text{H}_6\text{O}$ )<sub>b</sub> hydrophobic molecule (POP) and at least one

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polyxylylene unit is polyxyethylene ( $C_2H_4O$ )<sub>a</sub>, hydrophilic molecule (PEO). The block copolymer of POP and PEO may be used preferably as a triblock poly polymers having the general of trial ABA block copolymer formula as (PEO)<sub>a</sub>(POP)<sub>b</sub>(PEO)<sub>a</sub>, wherein the commercially available for “a in the range of 16-48 and “b” is in the range of 54-62 (line 4-16 on page 12 and lines 8-20 on page 19, Table 3). The Pluronic® (BASF), triblock polymer like F127 as recited in the instant application are also disclosed for practicing the invention. The total molecular weight of the copolymer can be 12,600 (see Table 2) and PEO block is about 30-50% in weight (see Table 3). The therapeutic agents disclosed in the cited prior art also include biological active material, such as viral antigen, bacterial toxoid, growth hormone etc. (see lines 14 on page 30 through line 3 on page 32). Other components, such as EDTA or Glycerin used as a routine drug excipient for enhancing the solubility and stability of the pharmaceutical composition are also disclosed (Table 4, and Table 8-11). Therefore, the claimed invention is anticipated by the cited prior art.

### ***Claim Rejections - 35 USC § 102***

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-31, 34, and 38-44 are rejected under 35 U.S.C. 102(e) as being anticipated by Balasubramanian et al. (b) (US Patent No. 6,416,947B1).

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Patent "947" teaches a composition comprising a polypropylene/polyxyethylen block polymer block, an immunogenic antigen and an adjuvant, wherein the high molecular weight of copolymer are useful as general surfactant to assist the antigen to be dissolved and absorbed by the host and display an enhanced biological efficacy as vaccine adjuvants. The block copolymer is consisting of polyxyethylene (POE,  $C_2H_4O$ ), which is hydrophilic, and polyxypropylen (POP,  $C_3H_6O$ ), which is hydrophobic. The block copolymer is built on a propylene glycol initiator. The biologically active copolymers have the following general formulation  $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ , wherein the "b" represents a number such that the molecular weight of the POP ( $C_3H_6O$ ) is approximately 7000-20,000 Daltons and the POE is between approximately 1%-40% by molecular weight. The antigen that can be used in the said vaccine composition include both DNA virus and RNA virus, bacterial antigen, tumor antigen, other microbial antigens, allergens, and other protein antigen, such as tetanus toxoid, peptide antigen etc (see col. 9, line 50 through col. 11, line 64). The composition is also disclosed for comprising oligonucleotides, antisense, triplex DNA compound, ribozyme in combination with the disclosed copolymer (claim 8). The composition further contains surfactant substances, such as Tween 80 (claim 9). Patent "947" also discloses a method of modifying an immune response to an antigen in a human or animal comprising administering the antigen admixed with an adjuvant, wherein the adjuvant consists of a polypropylene/polyxyethylen block polymer (see claim 10) and Qui-A sopanin etc. Moreover, Patent "947" teaches that variety of routes, including, but not limited to, intramuscular injection, intravenous injection, intraperitoneal injection, oral, rectal, vaginal, sublingually, and nasally, can be used for administering the composition comprising such polyxyethylene/polyxypropylene block copolymer (line 65 on col. 11 through line 3 on col. 12. and claim 50). Utilization of the composition comprising the said copolymer greatly enhances and prolongs the immune response (see Figures 9 and 23-24). Therefore, the claimed invention is anticipated by the cited prior art.

***Claim Rejections - 35 USC § 103***

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balasubramanian et al. (b) (US Patent No. 6,416,947B), Viegas et al. (a: US Patent No. 5,071,644 and B: 5,593,683), Illum et al (a: Pharmaceutical Research, 1994, Vol. 11, No. 1186-1189), Cox (Vaccine 1997, Vol. 15, pp. 248-256) and Horner et al. (Cellular Immunology 1998, Vol. 190, pp. 77-82).

Claimed invention indrawn to an immunogenic composition for accelerated and prolonged stimulation of the immune response comprising an antigen and a polymer, wherein the polymer has reverse-gelation transition temperature. The copolymer is a polyoxyalkylene block copolymer having a formula of  $\text{HO}(\text{C}_2\text{H}_4\text{O})_b(\text{C}_3\text{H}_6\text{O})_a(\text{C}_2\text{H}_4\text{O})_b\text{H}$  or  $\text{H}(\text{OC}_2\text{H}_2\text{CH}_2)_b(\text{OCHCH}_2)\text{CH}_3\text{a}(\text{OC}_2\text{H}_2\text{CH}_2)_b\text{OH}$ . The  $(\text{C}_3\text{H}_6\text{O})_a$  hydrophobic base has a molecular weight of at least about 400 and wherein the copolymer has an average molecular weight of about 12,600. The "a" is between 15 and 150 or 20-80, wherein the "b" is between 15-60. The antigen in the said antigen comprises from 0.00001% to 5% by weight of the composition, wherein the polymer comprises from 5 to 33% weight of the composition. The antigen includes many well-known pathogenic antigen or other protein or peptide antigen, such as HIV, HCV, Tetanus toxoid, HCG and tumor antigen etc. The composition also comprising a penetration enhancer, adjuvant, such as cytokine, CpG oligonucleotide, DDA etc.

Patent "947" teaches a composition comprising a polypropylene/polyoxyethylene block polymer block, an immunogenic antigen and an adjuvant, wherein the high molecular weight of copolymer are useful as general surfactant to assist the antigen to be dissolved and absorbed by the host and display an enhanced biological efficacy as vaccine adjuvants. The block copolymer is consisting of polyoxyethylene (POE,  $\text{C}_2\text{H}_4\text{O}$ ), which is hydrophilic, and polyoxypropylene (POP,  $\text{C}_3\text{H}_6\text{O}$ ), which is hydrophobic. The block copolymer is built on a propylene glycol initiator. The biologically active copolymers have the following general formulation  $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ , wherein the "b" represents a number such that the molecular

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weight of the POP ( $C_3H_6O$ ) is approximately 7000-20,000 Daltons and the POE is between approximately 1%-40% by molecular weight. The antigen that can be used in the said vaccine composition include both DNA virus and RNA virus, bacterial antigen, tumor antigen, other microbial antigens, allergens, and other protein antigen, such as tetanus toxoid, peptide antigen etc (see col. 9, line 50 through col. 11, line 64). The composition is also disclosed for comprising oligonucleotides, antisense, triplex DNA compound, ribozyme in combination with the disclosed copolymer (claim 8). The composition further contains surfactant substances, such as Tween 80 (claim 9). Patent "947" also discloses a method of modifying an immune response to an antigen in a human or animal comprising administering the antigen admixed with an adjuvant, wherein the adjuvant consists of a polypropylene/polyoxyethylene block polymer (see claim 10) and Quil-A saponin etc. Moreover, Patent "947" teaches that variety of routes, including, but not limited to, intramuscular injection, intravenous injection, intraperitoneal injection, oral, rectal, vaginal, sublingually, and nasally, can be used for administering the composition comprising such polyethylene/polyoxypropylene block copolymer (line 65 on col. 11 through line 3 on col. 12. and claim 50). Utilization of the composition comprising the said copolymer greatly enhances and prolongs the immune response (see Figures 9 and 23-24). Balasubramanian et al. is silence for polypropylene/polyoxyethylene block polymer being a temperature sensitive of reverse gelation and the composition comprising other adjuvant such as chitosan, cytokine, CpG motif, as well as DDA etc.

Viegas et al. filled several patents that disclosed that polypropylene/polyoxyethylene block polymer formulated as either  $HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$  or  $H(OC_2H_2CH_2)_b(OCHCH_2)CH_3a(OC_2H_2CH_2)_bOH$  is characterized as heat sensitive polymer. The aqueous mixture can be delivered to the area of the mammalian body as a form a semi-solid gel upon contact with mammalian body, and become low viscosity liquid at ambient temperatures (see col. 3, lines 5-10 in Viegas et al. a). The polyoxyethylene chain constituting at least about 60%, preferably, at least 70% by weight of the copolymer and the copolymer having a total average molecular weight, preferably at least 5000-15,000. Veigas et al. also teach that the heat sensitive polypropylene/polyoxyethylene block polymer can be used for polymerized many therapeutic agent, such as antibiotics or other drugs (see col. 6, lines 40 through con 7, line 65 of Viegas et al. b). Viegas do not teach that biological active material, such as pathogenic

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antigen or other vaccine component can be polymerized with the said heat sensitive copolymer and use of a penetration enhancer, such as chitosan or its derivatives in the pharmaceutical composition.

Illum et al. teach that chitosan and its derivatives are all well characterized pharmaceutical excipients in drug formulation to improve the dissolution of poorly soluble drug or for the sustained release of drugs. The mucosal adhesiveness property of chitosan has been used for developing a safe, efficient and reliable mucosal drug delivery vehicle for poorly absorbable drug such as proteins or peptides (a, see entire document).

Cox et al. teach that there are many agents that can be selected for using as an adjuvant to produce an enhanced immune response when it is formulated with an antigenic composition. The selection is dependent on the preferred antigen, the preferred target cells as well as the preferred immune response. For example, Avidine DDA is used for inducing Th1 immune response preferably (Table 4 on page 253), cytokine IL-2 is used for up-regulating Th1 immune response, whereas IL-4 is used for up-regulating Th2 immune response (Section of cytokine on page 252). Cox et al. does not teach the CpG motif.

Horner et al. teach that immunostimulatory sequence oligonucleotides (ISS-ODN) or call CpG motif is a potent mucosal adjuvant for inducing both mucosal and systemic Th1-biased immune response (see entire document).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited references and use the copolymer as disclosed by Patent "947" and Viegas et al. to make an immunogenic composition comprising the said copolymer in combination with other agent, which possess the immunological adjuvant activity, such as chitosan as taught by Illum et al., the CpG motif as disclosed by Horner or DDA or cytokine as taught by Cox et al. to see an enhanced and sustained immune response without unexpected results. Hence the claimed invention as a whole is prima facie obvious absence unexpected results.

19. Claims 1-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ron et al. (WO 98/06438), Illum et al. (a: Pharmaceutical Research, 1994, Vol. 11, No. 1186-1189), Cox et

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al. (Vaccine 1997, Vol. 15, pp. 248-256), Horner et al. (CELLULAR IMMUNOLOGY 1998, Vol. 190, pp. 77-82).

Claimed invention indrawn to an immunogenic composition for accelerated and prolonged stimulation of the immune response comprising an antigen and a polymer, wherein the polymer has reverse-gelation transition temperature. The copolymer is a polyoxyalkylene block copolymer having a formula of  $\text{HO}(\text{C}_2\text{H}_4\text{O})_b(\text{C}_3\text{H}_6\text{O})_a(\text{C}_2\text{H}_4\text{O})_b\text{H}$  or  $\text{H}(\text{OC}_2\text{H}_2\text{CH}_2)_b(\text{OCHCH}_2)\text{CH}_3\text{a}(\text{OC}_2\text{H}_2\text{CH}_2)_b\text{OH}$ . The  $(\text{C}_3\text{H}_6\text{O})_a$  hydrophobic base has a molecular weight of at least about 400 and wherein the copolymer has an average molecular weight of about 12,600. The "a" is between 15 and 150 or 20-80, wherein the "b" is between 15-60. The antigen in the said antigen comprises from 0.00001% to 5% by weight of the composition, wherein the polymer comprises from 5 to 33% weight of the composition. The antigen includes many well-known pathogenic antigen or other protein or peptide antigen, such as HIV, HCV, Tetanus toxoid, HCG and tumor antigen etc. The composition also comprising a penetration enhancer, chitosan or adjuvant etc.

Ron et al. Teach to use a heat sensitive polyalkylene copolymer as an immunogenic pharmaceutical vehicle to deliver many pharmaceutical compositions including many pathogenic antigens. The said vehicle is a block copolymer with different oxyalkylene units having a capacity of a reversible gelation at body temperature (25-40°C) (see line 11-24 on page 11). At least one polyalkylene unit is polyxypropylene  $(\text{C}_3\text{H}_6\text{O})_b$  hydrophobic molecule (POP) and at least one polyalkylene unit is polyxyethylene  $(\text{C}_2\text{H}_4\text{O})_a$ , hydrophilic molecule (PEO). The block copolymer of POP and PEO may be used preferably as a triblock polyalkylpolymers having the general of triblock ABA block copolymer formula as  $(\text{PEO})_a(\text{POP})_b(\text{PEO})_a$ , wherein the commercially available for "a" in the range of 16-48 and "b" is in the range of 54-62 (line 4-16 on page 12 and lines 8-20 on page 19, Table 3). The Pluronic® (BASF), triblock polymer like F127 as recited in the instant application are also disclosed for practicing the invention. The total molecular weight of the copolymer can be 12,600 (see Table 2) and PEO block is about 30-50% in weight (see Table 3). The therapeutic agents disclosed in the cited prior art also include biological active material, such as viral antigen, bacterial toxoid, growth hormone etc. (see lines 14 on page 30 through line 3 on page 32). Other components, such as EDTA or Glycerin used as

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a routine drug excipient for enhancing the solubility and stability of the pharmaceutical composition are also disclosed (Table 4, and Table 8-11). Ron et al. do not teach that chitosan and its derivatives can be used with copolymer to enhance penetration and reaction in the composition.

Illum et al. teach that chitosan and its derivatives are all well characterized pharmaceutical excipients in drug formulation to improve the dissolution of poorly soluble drug or for the sustained release of drugs. The mucosal adhesive property of chitosan has been used for developing a safe, efficient and reliable mucosal drug delivery vehicle for poorly absorbable drug such as proteins or peptides (a, see entire document).

Cox et al. teach that there are many agents that can be selected for using as an adjuvant to produce an enhanced immune response when it is formulated with an antigenic composition. The selection is dependent on the preferred antigen, the preferred target cells as well as the preferred immune response. For example, Avidine DDA is used for inducing Th1 immune response preferably (Table 4 on page 253), cytokine IL-2 is used for up-regulating Th1 immune response, whereas IL-4 is used for up-regulating Th2 immune response (Section of cytokine on page 252). Cox et al. does not teach the CpG motif.

Horner et al. teach that immunostimulatory sequence oligonucleotides (ISS-ODN) or call CpG motif is a potent mucosal adjuvant for inducing both mucosal and systemic Th1-biased immune response (see entire document).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was filed to be motivated by the recited references and use the copolymer as disclosed by Ron et al. to make an immunogenic composition comprising the said copolymer in combination with other agent, which possess the immunological adjuvant activity, such as chitosan as taught by Illum et al., the CpG motif as disclosed by Horner or DDA or cytokine as taught by Cox et al. to see an enhanced and sustained immune response without unexpected results. Hence the claimed invention as a whole is prima facie obvious absent unexpected results.

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*Conclusion*

No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 8:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bao Qun Li

October 18, 2002



ALI R. SALIMI  
PRIMARY EXAMINER